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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/691,672 | 10/24/2003 | Pierre Druilhe | 2356.0085 | 1306 |

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| EXAMINER | |
|---|---|
| GANGLE, BRIAN J | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1645 | |

DATE MAILED: 09/27/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/691,672 | DRUILHE, PIERRE | |
| | Examiner | Art Unit | |
| | Brian J. Gangle | 1645 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *19 January 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *18-35* is/are pending in the application.

4a) Of the above claim(s) *24-26 and 34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18-23,27,28 and 35* is/are rejected.

7)☒ Claim(s) *29-33* is/are objected to.

8)☒ Claim(s) *18-35* are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 October 2003* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/26/04, 4/26/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

### *Drawings*

New corrected drawings are required in this application because the edges of figures 1, 3, 9, 11, and 12 are cut off. Additionally, figure 4 contains panels 4a, 4b, and 4c which are not described specifically in the brief description of drawings. Further, figures 11 and 12 contain indices which are not written in English. The corrected drawings are required in reply to the Office action to avoid abandonment of the application. The requirement for corrected drawings will not be held in abeyance.

### *Sequence Requirements*

This application fails to comply with the requirements of 37 C.F.R. 1.821-1.825 because it contains amino acid sequences that are not identified. For example, page 39, lines 11-12, contain a sequence that is not identified. Appropriate sequence identifiers should be used to comply with sequence rules. The sequences in the specification should match the sequence listing and computer readable form (CRF) submitted with the application. Applicant is asked to review the specification for sequences that are not identified and correction is required. Applicant must provide a substitute computer readable form (CRF) copy of the "Sequence Listing", a substitute paper copy of the "Sequence Listing", an amendment of the specification to insert appropriate sequence identifiers, and a statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

### *Specification*

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code on page 39, line 12 of the specification. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required: Claim 23 refers to a chimeric molecule which is a "synthetic" peptide. This issue is best resolved by applicant pointing to the specification by page and line number where antecedent basis can be found.

The use of the trademark MONTANIDE™ has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892 or the current 1449 of record, they have not been considered.

***Information Disclosure Statement***

The information disclosure statements filed on 2/26/2004 and 4/26/2005 have been considered. Initialed copies are enclosed. Theisen *et al.*, cited on the IDS of 4/26/2005 was not considered because it was already of record and considered with the IDS filed on 2/26/2004.

***Election/Restrictions***

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 18-23, 29-33, and 35, drawn to chimeric molecules and vaccines, classified in class 424, subclass 191.1.

II. Claims 24-26, and 29-33, drawn to conjugates comprising conjugates of chimeric molecules bound to a support, classified in class 424, subclass 191.1.

III. Claims 29-33, drawn to a mixture of GLURP and MSPS antigens, classified in class 424, subclass 191.1.

IV. Claim 34, drawn to antibodies for passive immunotherapy of malaria, classified in class 424, subclass 139.1.

Claims 27-28 link Inventions I (Claims 18-23, 29-33, and 35), II (Claims 24-26 and 29-33), and Invention III (Claims 29-33). The restriction requirement among the linked inventions is subject to the nonallowance of the linking claim(s). Upon the allowance of the linking claim(s), the restriction requirement as to the linked inventions shall be withdrawn and any claim(s) depending from or otherwise including all the limitations of the allowable linking claim(s) will be entitled to examination in the instant application. Applicant(s) are advised that if any such claim(s) depending from or including all the limitations of the allowable linking claim(s) is/are presented in a continuation or divisional application, the claims of the continuation or divisional application may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application. Where a restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. *In re Ziegler*, 44 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

The inventions are distinct, each from the other because of the following reasons:

Inventions I and II are related as products. The claims of Invention I are drawn to chimeric molecules and vaccines, while the claims of Invention II are drawn to conjugates comprising chimeric molecules bound to a support. The inventions are patentably distinct products because they are made by different methods and because they are physically and functionally distinct chemical entities.

Inventions I and III are related as products. The claims of Invention I are drawn to chimeric molecules and vaccines, while the claims of Invention III are drawn to a mixture of GLURP and MSPS antigens. The inventions are patentably distinct products because they are made by different methods and because they are physically and functionally distinct chemical entities.

Inventions I and IV are related as products. The claims of Invention I are drawn to chimeric molecules and vaccines, while the claims of Invention IV are drawn to antibodies for passive immunotherapy of malaria. The inventions are patentably distinct products because they are made by different methods and because they are physically and functionally distinct chemical entities with no common core structure.

Inventions II and III are related as products. The claims of Invention II are drawn to conjugates comprising chimeric molecules bound to a support, while the claims of Invention III are drawn to a mixture of GLURP and MSPS antigens. The inventions are patentably distinct products because they are made by different methods and because they are physically and functionally distinct chemical entities and the mixture is not required to make the chimeric molecule or conjugate.

Inventions II and IV are related as products. The claims of Invention II are drawn to conjugates comprising chimeric molecules bound to a support, while the claims of Invention IV are drawn to antibodies for passive immunotherapy of malaria. The inventions are patentably distinct products because they are made by different methods and because they are physically and functionally distinct chemical entities with no common core structure.

Inventions III and IV are related as products. The claims of Invention III are drawn to a mixture of GLURP and MSPS antigens, while the claims of Invention IV are drawn to a medicament for passive immunotherapy of malaria. The inventions are patentably distinct products because they are made by different methods and because they are physically and functionally distinct chemical entities with no common core structure.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter, restriction for examination purposes as indicated is proper.

During a telephone conversation with William Raich on 7/27/2005 a provisional election was made without traverse to prosecute the invention of Group I, claims 18-23, 35 and linking claims 27-33. Affirmation of this election must be made by applicant in replying to this Office action. Claims 24-26 and 34 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

***Claim Objections***

Claims 29-33 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from any other multiple dependent claim. See MPEP § 608.01(n). Accordingly, the claims have not been further treated on the merits.

Claims 18, 20-21, 27-28, and 35 are objected to because of the following informalities: claims contain the acronyms GLURP, MSP-3. While acronyms are permissible shorthand in claims, the first recitation should include the full recitation followed by the acronym in parenthesis. Appropriate correction is required.

Claim 23 objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The word synthetic is defined by The American Heritage® Dictionary of the English Language: Fourth Edition, 2000, as "**1.** Relating to, involving, or of the nature of synthesis. **2.** *Chemistry* Produced by synthesis, especially not of natural origin. **3a.** Not natural or genuine; artificial or contrived: *"counterfeit rhetoric that flourishes when passions are synthetic"* (George F. Will). **b.** Prepared or made artificially: *synthetic leather.*" A recombinant fusion protein is not natural and is biochemically synthesized. The synthetic peptide of claim 23 meets all of the limitations of the parent claim, claim 21, and is therefore not further limiting.

Claims 27-28 are objected to because of the following informalities: claims are dependent on claim 24 which is drawn to a non-elected invention. Appropriate correction is required.

***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 18, 27-28 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 3-11 of Druilhe *et al.* (U.S. Patent No. 6,017,538) in view of Theisen *et al.* (Infect. Immun. 69:5223-5229, 2001), and Shi *et al.* (Vaccine, 18:2902-2914, 2000).

Claim 18 is drawn to a chimeric molecule comprising a GLURP moiety comprising a variant of a polypeptide fragment of at least 50 amino acids from the $GLURP_{25-514}$ fragment and a MSP3 moiety comprising a polypeptide fragment of at least 50 amino acids from the $MSP3_{212-380}$ fragment wherein said chimeric molecule raises antibodies against both the $GLURP_{24-514}$ fragment and $MSP3_{212-380}$ fragment in mice immunized with it, wherein either or both moieties can have 1-15 amino acids deleted, added, or changed by conservative substitution. As such, a polypeptide comprising a GLURP moiety and an MSP3 moiety comprising 35 amino acids from SEQ ID 2 would meet the limitations of the claim. Claims 27 and 28 are drawn to an immunogenic composition comprising (claim 27) and a vaccine comprising as an immunogen

(claim 28) the chimeric molecule of claim 18 or a conjugate comprising the chimeric molecule of claim 18 which is bound to a support.

Druilhe *et al.* teach (in claims 1, and 3-7) a purified MSP3 polypeptide fragment of 65 amino acids, 47 of which are 100% identical to residues 212-257 of SEQ ID 2. Druilhe *et al.* further teaches said molecule bound to a support (claim 8), as an immunogenic composition (claims 9-10), and as a vaccine (claim 11). Druilhe *et al.* differs from the instant application by not teaching the chimeric molecule as comprising both an MSP3 fragment and GLURP fragment wherein the chimeric molecule raises antibodies against both MSP3 and GLURP fragments.

Theisen *et al.* teach two synthetic GLURP fragments, $GLURP_{85\text{-}213}$ and $GLURP_{191\text{-}287}$ that raise, in mice immunized with them, antibodies to said fragments (p. 5224, col. 1, paragraph 2 and p. 5226, paragraph bridging columns 1 and 2).

Shi *et al.* teach that by combining epitopes identified through *in vitro* and *in vivo* studies in model systems, one can create a multivalent synthetic (fusion) malaria vaccine with a higher level of protection that that provided by single component vaccine (p. 2911, col. 2, paragraph 1).

As to claim 18 and 28-28, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time of invention to combine, with a reasonable expectation of success, the synthetic $GLURP_{85\text{-}213}$ fragment of Theisen *et al.* and the MSP3 polypeptide, as well as a synthetic fragment of that peptide that includes the identified epitope ($MSP3_{211\text{-}237}$) of Druilhe *et al.* into the chimeric molecule and immunogenic compositions of the instant application because Shi *et al.* teaches that combining these epitopes would create a multivalent synthetic (fusion) malaria vaccine with a higher level of protection that that provided by single component vaccine. Said combination of peptides would give a molecule that, when tested in the manner set forth in the instant specification, would raise anti-MSP3 and anti-GLURP in mice immunized with it.

Claims 18 and 27-28 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of copending Application No. 10/774,602 (Druilhe) in view of Theisen *et al.* (Infect. Immun. 69:5223-5229, 2001), and Shi *et al.* (Vaccine, 18:2902-2914, 2000).

Claim 18 is drawn to a chimeric molecule comprising a GLURP moiety comprising a variant of a polypeptide fragment of at least 50 amino acids from the $GLURP_{25-514}$ fragment and a MSP3 moiety comprising a polypeptide fragment of at least 50 amino acids from the $MSP3_{212-380}$ fragment wherein said chimeric molecule raises antibodies against both the $GLURP_{24-514}$ fragment and $MSP3_{212-380}$ fragment in mice immunized with it, wherein either or both moieties can have 1-15 amino acids deleted, added, or changed by conservative substitution. As such, a polypeptide comprising a GLURP moiety and an MSP3 moiety comprising 35 amino acids from SEQ ID 2 would meet the limitations of the claim. Claims 27 and 28 are drawn to an immunogenic composition comprising (claim 27) and a vaccine comprising as an immunogen (claim 28) the chimeric molecule of claim 18

Druilhe teaches (in claim 1) a purified MSP3 polypeptide fragment of 68 amino acids comprising a combination of the MSP-3b peptide (SEQ ID No: 12), MSP-3c peptide (SEQ ID No: 13), and MSP-3d peptide (SEQ ID No: 14), 67 of which are 100% identical to residues 212-228 of SEQ ID 2. Druilhe further teaches long synthetic or recombinant polypeptide comprising epitopes contained within a MSP-3b peptide (SEQ ID No: 12), a MSP-3c peptide (SEQ ID No: 13), or a MSP-3d peptide (SEQ ID No: 14) and combinations of said peptides (claim 2), an immunogenic composition comprising a long synthetic or recombinant polypeptide comprising epitopes contained within the MSP3b, MSP3c, or MSP3d polypeptides which together correspond to amino acids 212-278 of the MSP3 fragment of the instant application (claim 3), and a vaccine comprising said MSP3 molecule and a pharmaceutically acceptable carrier (claim 4). Druilhe *et al.* differs from the instant application by not teaching said peptides as a chimeric molecule comprising both an MSP3 fragment and GLURP fragment that raises antibodies against both MSP3 and GLURP fragments.

Theisen *et al.* teach two synthetic GLURP fragments, $GLURP_{85-213}$ and $GLURP_{191-287}$ that raise, in mice immunized with them, antibodies to said fragments (p. 5224, col. 1, paragraph 2 and p. 5226, paragraph bridging columns 1 and 2).

Shi *et al.* teach that by combining epitopes identified through *in vitro* and *in vivo* studies in model systems, one can create a multivalent synthetic (fusion) malaria vaccine with a higher level of protection that that provided by single component vaccine (p. 2911, col. 2, paragraph 1).

As to claims 18 and 27-28, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time of invention to combine, with a reasonable expectation of success, the synthetic $GLURP_{85-213}$ fragment of Theisen *et al.* and the MSP3 fragment polypeptide, of Druilhe into the chimeric molecule and immunogenic composition of the instant application because Shi *et al.* teaches that combining these epitopes would create a multivalent synthetic (fusion) malaria vaccine with a higher level of protection that that provided by single component vaccine. Said combination of peptides would give a molecule that, when tested in the manner set forth in the instant specification, would raise anti-MSP3 and anti-GLURP in mice immunized with it.

This is a provisional obviousness-type double patenting rejection.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 18-23, 27-28, and 35 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

As to claims 18, 35, and dependent claims 19-23, 27-28, claims 18 and 35 are drawn to chimeric molecules comprising a GLURP moiety comprising at least 50 amino acids from the $GLURP_{27-500}$ fragment fused to a MSP3 moiety comprising at least 50 amino acids from the $MSP3_{212-380}$ fragment or a variant thereof in which 1 to 15 amino acids in any or both of said moieties have been deleted, added, or changed by conservative substitution. The specification discloses the following chimeric molecules: $GLURP_{25-500}|MSP3_{212-382}$, $GLURP_{27-500}|MSP3_{212-380}$, and $GLURP_{25-514}|MSP3_{212-380}$. No written description is provided for variants in which 1 to 15 amino acids have been deleted, added or changed by conservative substitution. Further, the molecules described only have deletions or additions on the ends of the individual moieties. There are no substitutions or changes internal to the fragments described. The recitation of "at least 50 amino acids from" and "variants in which 1 to 15 amino acids have been deleted, added or changed by conservative substitution" does not convey a common structure or function. The scope of the claims includes numerous structural variants, and the genus is highly variant because a significant number of structural differences between genus members is permitted. The specification provides no guidance on the structure of the polypeptide or what changes can or cannot be made. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general guidance is needed. Since the disclosure fails to describe the common attributes or structural characteristics that identify members of the genus, and because the genus is highly variant, the function of immunogenicity alone is insufficient to describe the genus of chimeric GLURP/MSP3 molecules as claimed in the instant application. One of skill in the art would reasonably conclude that the disclosure of a single SEQ ID fails to provide a representative number of species to describe the claimed genus, and as such, the specification lacks written description for the highly variant genus chimeric GLURP/MSP3 molecules and one skilled in the art would not recognize that applicants had possession of the genus of claimed polypeptides for use as instantly claimed.

As to claims 20-23, claims 20 and 21 are drawn to a chimeric molecule which, in claim 20 raises higher levels of anti-MSP3 antibodies than either the $MSP3_{212-380}$ fragment or a mixture of the $GLURP_{25-514}$ fragment and the $MSP3_{212-380}$ fragment, and in claim 21 raises higher levels of anti-GLURP antibodies than either the $GLURP_{25-514}$ fragment or a mixture of the $GLURP_{25-514}$ fragment and the $MSP3_{212-380}$ fragment. In the specification, the chimeric molecule is not

compared to either the $MSP3_{212-380}$ fragment or the $GLURP_{25-514}$ fragment alone. The hybrid is only compared to an injection containing both GLURP and MSP3 fragments, or to separate injections of the GLURP and MSP3 fragments in the same animal. In addition, 20$\mu$g of hybrid was compared with 15$\mu$g of the $GLURP_{25-514}$ fragment and 5$\mu$g of the $MSP3_{212-380}$ fragment. As stated in Hanly *et al.* (ILAR Journal V37(3), 1995, p. 13, paragraph 3), within a window of immunogenicity, a larger dose of antigen generally results in a greater antibody response. Thus, the comparison presented in the claims is not supported by the specification and is not a valid comparison. Further, the antibodies which applicants test for are only to the $GLURP_{25-514}$ fragment and the $MSP3_{212-380}$ fragment. The claims are based on the $GLURP_{25-514}$ fragment and the $MSP3_{212-380}$ fragment, and are tested against anti-MSP3 and anti-GLURP antibodies, which appear to be the entire proteins. The specification does not provide for the comparison presented in the claims since the GLURP and MSP3 fragments were only tested against antibodies to themselves, rather than to the whole GLURP and MSP3 proteins as stated in the claims.

Claims 18-23, 27-28, and 35 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a chimeric molecule consisting of either the $GLURP_{25-500}$ and $MSP3_{212-382}$ fragments, the $GLURP_{27-500}$ and $MSP3_{212-380}$ fragments, or the $GLURP_{25-514}$ and $MSP3_{212-380}$ fragments, and immunogenic compositions comprising said chimeric molecules, does not reasonably provide enablement for a chimeric molecule comprising a GLURP moiety comprising a polypeptide fragment of at least 50 amino acids from the $GLURP_{25-514}$ fragment of SEQ ID NO:1, and a MSP3 moiety comprising a polypeptide fragment of at least 50 amino acids from the $MSP3_{212-380}$ fragment of SEQ ID NO:2, or a variant thereof in which 1 to 15 amino acids in any or both of said moieties have been deleted, added, or changed by conservative substitution, or a vaccine comprising said chimeric molecule. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

As to claims 18-23, 27-28, and 35, claims 18 and 35 recite chimeric molecules comprising two moieties of at least 50 amino acids of the GLURP and MSP3 fragments wherein any 1-15 amino acids in either or both moieties have been deleted, added, or changed, and that said molecule is capable of raising antibodies against the polypeptides of SEQ ID's 1 and 2.

However, other than the specific chimeric molecules consisting of $GLURP_{25-500}$ and $MSP3_{212-382}$ fragments, the $GLURP_{27-500}$ and $MSP3_{212-380}$ fragments, or the $GLURP_{25-514}$ and $MSP3_{212-380}$ fragments, the specification fails to disclose any other peptide with said immunogenic activity. Further, while the art provides several regions within these fragments which are important epitopes (Oeuvray *et al.*, Blood, 84:1594-1602, 1994 and Theisen *et al.*, Vaccine, 19:204-212, 2001), the specification provides no guidance to which specific 50 amino acids should be included in said molecule. Additionally, there is no guidance as to which 1-15 amino acids can be altered without affecting the immunogenicity of the molecule. Theisen *et al.* teach that there are epitopes as short as 13 amino acids (abstract) in the GLURP fragment, showing that alteration of 15 amino acids can significantly alter the immunogenicity of the molecule. Moreover, protein chemistry is one of the most unpredictable areas of biotechnology and the art teaches that the significance of any particular amino acid and sequence for different aspects of biological activity cannot be predicted *a priori* and must be determined empirically on a case by case basis (Rudinger *et al.* in "Peptide Hormones", ed. Parsons, J.A., University Park Press, 1976, p. 6). The art specifically teaches that even a single amino acid change in a protein leads to unpredictable changes in the biological activity of the protein. For example, McGuinness *et al.* (Lancet, 337:514-517, March 1991, abstract and p. 514) taught that a point mutation generating a single amino acid change in a P1.16-specific epitope in the VR2 region of the *porA* gene of a strain of *Neisseria meningitidis* of subtype P1.7,16 resulted in "striking changes in the structural and immunological properties of the class 1 protein" of this isolate. Additionally, Houghten *et al.* (New Approaches to Immunization, Vaccines86, Cold Spring Harbor Laboratory, p. 21-25, 1986) taught the criticality of individual amino acid residues and their positions in peptide antigen-antibody interactions. Houghten *et al.* state (p. 24): "One could expect point mutations in the protein antigen to cause varying degrees of loss of protection, depending on the relative importance of the binding interaction of the altered residue. A protein having multiple antigenic sites, multiple point mutations, or accumulated point mutations at key residues could create a new antigen that is precipitously or progressively unrecognizable by any of the antibodies in the polyclonal pool." These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification, will often dramatically affect the biological activity of a protein. Proteins with replacement of a single

amino acid residue may lead to both structural and functional changes in biological activity and immunological recognition. Applicants have not taught which residues of SEQ ID's 1 and 2 can be varied and still achieve a protein that is capable of use as claimed. Because of this lack of guidance, it would require extended experimentation for the skilled artisan to arrive at chimeric molecules other than those specifically listed in the specification (i.e. chimeric molecules consisting of $GLURP_{25\text{-}500}$ and $MSP3_{212\text{-}382}$ fragments, the $GLURP_{27\text{-}500}$ and $MSP3_{212\text{-}380}$ fragments, or the $GLURP_{25\text{-}514}$ and $MSP3_{212\text{-}380}$ fragments) and therefore, the full scope of the claims are not enabled.

As to claim 28, the claim is drawn to a vaccine against malaria. As of the time of invention, the art has shown no effective malaria vaccine in humans, only candidates that have not yet proven effective in preventing infection (Carvalho *et al.*, Scand. J. of Immunol., 56:327-343, 2002, abstract)(Perlman *et al.*, Malaria Immunology, 2002, p. 262, paragraph 2)(Ballou *et al.*, Am. J. Trop. Med. Hyg. 71:239-247, 2004, p. 239, abstract). As stated by Druilhe *et al.* (U.S. Pat. Pub. 2004/0096466, p. 1, paragraph 0015): "The research approach most often taken in the development of a vaccine against malaria due to P. falciparum hence consists of the identification (on the basis of the information cited above) of a potential candidate and then the evaluation of its value either in vitro by testing the specific antibodies in the inhibition of the growth of the parasite or of certain of its properties (cytoadhesion, rosette formation . . . ), or in vivo by the immunization of monkeys often with the complete Freund adjuvant. The present situation may thus be summed up as the existence of a large number of potential candidates characterized by their biochemical properties, their nucleotide and protein sequences, their degree of polymorphism, their localization on the parasite etc. Nevertheless, the researchers dispose of limited means for assessing the value of their candidates: 1) in vitro tests implicating mechanisms of action of antibodies whose validity in vivo is poorly documented, 2) vaccinations of non-human primates, and hence the evaluation of the effect of a vaccine on an experimental infection is based on parasitological and clinical parameters and particularly the type of immunity which may be induced which are very different from those of the natural infection in man". The parasite that causes malaria (*Plasmodium*) has a complex life cycle including several stages both in the mosquito vector and in humans. Infection in humans begins when the bite of an infected mosquito spreads sporozoites into the human where they invade cells in the liver.

During this stage, infections are asymptomatic. After a length of time that varies with species, the sporozoites develop into merozoites and release from the liver in order to infect red blood cells. Clinical disease occurs at this stage as changes in red blood cells and the immune response cause damage to the human host. The vaccine of the instant application is drawn to antigens from the erythrocyte (red blood cell) stage and does not prevent infection of the liver by the sporozoites, thus allowing the parasite to infect and continue to re-infect the bloodstream. While the components of the chimeric molecule claimed in the instant application are associated with a type of naturally acquired immunity called premunition, wherein adults chronically harbor low-grade parasitemia with occasional malarial episodes (Soe-Soe *et al.*, Trans. Royal Soc. Trop. Med. Hyg. 95:81-84, 2001, col. 1, paragraph1), the chimeric molecule and the GLURP-MSP3 mixture vaccines as claimed have not been shown through human or animal challenge experiments to provide protection against infection (the Dictionary of Biochemistry and Molecular Biology, Stenesh, 1989, defines a vaccine as a suspension of antigens that are derived from infectious bacteria or viruses and that, upon administration to humans or to animals, will produce active immunity and will provide protection against infection by these, or by related, bacteria or viruses). There are three lines of evidence given in the specification of the putativ efficacy of said vaccine. First, anti-GLURP and anti-MSP3 antibodies can inhibit parasite growth *in vitro*. Second, there is an association between premunition and the GLURP and MSP3 antigens. Third, transfer of anti-GLURP and anti-MSP3 antibodies in an immunocompromised mouse model can clear parasitemia from the bloodstream. However, while those of skill in the art recognize that *in vitro* assays and or cell-cultured based assays are somewhat useful to observe basic physiological and cellular phenomenon such as screening the effects of potential drugs, clinical correlations are generally lacking. The greatly increased complexity of the *in vivo* environment as compared to the very narrowly defined and controlled conditions of an *in vitro* assay does not permit a single extrapolation of *in vitro* assays to *in vivo* efficacy with any reasonable degree of predictability. *In vitro* assays cannot easily assess cell-cell interactions that may be important in a particular pathological state. Furthermore it is well known in the art that cultured cells, over a period time, lose phenotypic characteristics associated with their normal counterpart cell type. Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, page 4) teach that it is recognized in the art that there are many

differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation in vivo. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences In Vitro). Also, a person in the state of premunition, which is associated with the antigens of the instant application, is not, in fact, protected from malarial infection or parasitemia. Additionally, the clearing of parasitemia by anti-GLURP and anti-MSP3 antibodies in immunocompromised mice does not remove the infection from the mice, it only removes the erythrocytic infection, leaving parasites in the liver to continue to cause parasitemia in the future. In view of the lack of support in the art and specification for an effective vaccine against malaria, it would require undue experimentation to make and use the vaccine as claimed; therefore the entire scope of the claim is not enabled.

Claims 19-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

As to claim 19 and dependent claims 20-23, claim 19 is drawn to a chimeric molecule which is "more immunogenic than a mixture of the polypeptides of SEQ ID's 1 and 2". There is no definition in the specification of the phrase "more immunogenic". How is immunogenicity measured in this case? If applicant means that said molecule causes higher levels of antibodies, as mentioned in claims 20 and 21, then claim 19 should state this. However, claims 20 and 21 refer to a chimeric molecule which, in claim 20 raises higher levels of anti-MSP3 antibodies than either the $MSP3_{212-380}$ fragment or a mixture of the $GLURP_{25-514}$ fragment and the $MSP3_{212-380}$ fragment, and in claim 21 raises higher levels of anti-GLURP antibodies than either the $GLURP_{25-514}$ fragment or a mixture of the $GLURP_{25-514}$ fragment and the $MSP3_{212-380}$ fragment. It is unclear how this "higher level" of antibodies (and thus immunogenicity?) is being measured. In the disclosed examples, 20$\mu$g of the hybrid protein was compared to only 15$\mu$g of

$GLURP_{25\text{-}514}$ and 5$\mu$g of $MSP3_{212\text{-}380}$. As taught in Hanly *et al.* (ILAR Journal V37(3), 1995), the more antigen added, the greater the antibody response will be. Therefore, since the amounts of the GLURP fragment and MSP3 fragment tested were not equal to that of the hybrid, it is unclear what was tested and therefore it is unclear what "more immunogenic" means or how it is measured.

***Claim Rejections - 35 USC § 102 and 103***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 18-23, 27-28, and 35 are rejected under 35 U.S.C. 102(a) as being anticipated by Theisen *et al.* (Vaccine 22:1188-1198. 2004. on-line Oct. 20, 2003).

As to claims 18-22, and 35, Theisen *et al.* teach a chimeric molecule comprising a GLURP moiety consisting of a $GLURP_{27\text{-}500}$ fragment fused to a $MSP3_{212\text{-}380}$ fragment, wherein the molecule raises antibodies against both $GLURP_{25\text{-}514}$ and $MSP3_{212\text{-}380}$ fragments (figure 4, p.

1195). Theisen *et al.* further teach the same chimeric molecule wherein the molecule raises, in mice immunized with it, higher levels of anti-MSP3 and anti-GLURP antibodies than a mixture of both the $GLURP_{25-514}$ and $MSP3_{212-380}$ fragments (figure 4, p. 1195). Theisen *et al.* also teach that said chimeric molecule raises, in mice immunized with it, IgG antibodies that can inhibit parasite growth *in vitro* in cooperation with human monocytes as shown by an ADCI assay (section 3.5, page 1195).

As to claim 23, Theisen *et al.* teach a chimeric molecule comprising a GLURP moiety consisting of a $GLURP_{27-500}$ fragment fused to a $MSP3_{212-380}$ fragment, wherein the molecule raises, in mice immunized with it, higher levels of anti-MSP3 and anti-GLURP antibodies than a mixture of both the $GLURP_{25-514}$ and $MSP3_{212-380}$ fragments (figure 4, p. 1195). While Theisen *et al.* does not specifically teach the peptide (chimeric molecule) as a synthetic peptide, the patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process. Additionally, as set forth *supra* a recombinant fusion protein is not natural and is biochemically synthesized, therefore, the product of claim 23 is taught by Theisen *et al.*

As to claims 27-28, Theisen *et al.* teach an immunogenic composition comprising a chimeric molecule comprising a GLURP moiety consisting of a $GLURP_{27-500}$ fragment fused to a $MSP3_{212-380}$ fragment, wherein the molecule raises antibodies against both $GLURP_{25-514}$ and $MSP3_{212-380}$ fragments (figure 4, p. 1195). Theisen *et al.* further teach said composition in association with a suitable pharmaceutical vehicle (Montanide™ ISA720)(section 2.5, p. 1191).

Claims 18- , 27-28, and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Oeuvray *et al.* (Blood, 84:1594-1602, 1994) in view of Theisen *et al.* (Infect. Immun. 69:5223-5229, 2001), Hanly *et al.* (ILAR Journal V37(3), 1995), and Shi *et al.* (Vaccine, 18:2902-2914, 2000).

The instant claims are drawn to a chimeric molecule comprising a GLURP moiety comprising a polypeptide fragment of at least 50 amino acids from the $GLURP_{25-514}$ fragment and a MSP3 moiety comprising a polypeptide fragment of at least 50 amino acids from the $MSP3_{212-380}$ fragment wherein said chimeric molecule raises antibodies against both the

$GLURP_{24-514}$ fragment and $MSP3_{212-380}$ fragment in mice immunized with it (claim 18). The instant claims further include an immunogenic composition comprising as an immunogen a chimeric molecule according to claim 18 (claim 27), a vaccine against malaria comprising as an immunogen a chimeric molecule according to claim 18, in association with a suitable pharmaceutical vehicle (claim 28), and chimeric molecule comprising a GLURP moiety consisting of a polypeptide fragment of at least 50 amino acids from the $GLURP_{25-514}$ fragment of SEQ ID NO:1 ($GLURP_{24-514}$), and a MSP3 moiety consisting a polypeptide fragment of at least 50 amino acids from the $MSP3_{212-380}$ fragment of SEQ ID NO:2 ($MSP3_{212-380}$), or a variant thereof in which 1 to 15 amino acids in any or both of said moieties have been deleted, added, or changed by conservative substitution, wherein said chimeric molecule raises antibodies against both the polypeptides of SEQ ID NO:1 and SEQ ID NO:2 in mice immunized with it (claim 35).

Oeuvray *et al.* teach the MSP3 peptide, as well as a synthetic fragment of that peptide ($MSP3_{211-237}$) that serves as an epitope in MSP3 and raises, in mice immunized with it, antibodies to said fragment ($MSP3_{211-237}$) (p. 1595, col. 1, paragraph 5, and p. 1600, paragraph bridging col. 1 and 2). It is further taught that antibodies raised in a mammal (humans and mice) can inhibit parasite growth *in vitro* in cooperation with human monocytes (p. 1597, figure 2C). Oeuvray *et al.* also teach said molecules as an immunogenic composition in a suitable pharmaceutical vehicle (p. 1595, col. 2, paragraph 2) and suggest that said molecule may be useful as a vaccine against malaria (p. 1601, col. 2, paragraph 1). Oeuvray *et al.* differs from the instant application by not teaching a chimeric molecule comprising both an MSP3 fragment and GLURP fragment that raises antibodies against both MSP3 and GLURP fragments. Theisen *et al.* teach two synthetic GLURP fragments, $GLURP_{85-213}$ and $GLURP_{191-287}$ that raise, in mice immunized with them, antibodies to said fragments (p. 5224, col. 1, paragraph 2 and p. 5226, paragraph bridging columns 1 and 2). Theisen *et al.* further teach said fragments as an immunogenic composition in a suitable pharmaceutical vehicle (p. 5226, paragraph bridging columns 1 and 2). The authors further suggest that $GLURP_{85-213}$ can be used in humans with an appropriate adjuvant to protect against malaria (a vaccine) (p. 5228, col. 2, paragraph 1).

Shi *et al.* teach that by combining epitopes identified through *in vitro* and *in vivo* studies in model systems, one can create a multivalent synthetic (fusion) malaria vaccine with a higher level of protection that that provided by single component vaccine (p. 2911, col. 2, paragraph 1).

As to claims 18, 27-28, and 35, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time of invention to combine, with a reasonable expectation of success, the synthetic $GLURP_{85-213}$ fragment of Theisen *et al.* and the MSP3 peptide, as well as a synthetic fragment of that peptide that includes the identified epitope ($MSP3_{211-237}$) of Oeuvray *et al.* into the chimeric molecule and immunogenic composition of the instant application because Shi *et al.* teaches that combining these epitopes would create a multivalent synthetic (fusion) malaria vaccine with a higher level of protection that that provided by single component vaccine. Said combination of peptides would give a molecule that would raise antibodies against both the $GLURP_{24-514}$ fragment and $MSP3_{212-380}$ fragment in mice immunized with it.

Claims 19-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Oeuvray *et al.* (Blood, 84:1594-1602, 1994), Theisen *et al.* (Infect. Immun. 69:5223-5229, 2001), and Shi *et al.* (Vaccine, 18:2902-2914, 2000) as applied to claims 18, 27-28, and 35 above, and further in view of Hanly *et al.* (ILAR Journal V37(3), 1995).

Oeuvray *et al.*, Theisen *et al.*, and Shi *et al.* as combined over claims 18, 27-28, and 35 is set forth *supra*. The combination as set forth *supra* does not teach that said chimeric molecule is more immunogenic than a mixture of the $GLURP_{24-514}$ fragment and $MSP3_{212-380}$ fragment (claim 19) and raises higher levels of anti-MSP3 antibodies (claim 20) and higher levels of anti-GLURP antibodies (claim 21) than a mixture of the $GLURP_{24-514}$ fragment and $MSP3_{212-380}$ fragment. The combination as set forth *supra* does teach said fragment would, as taught by Oeuvray *et al.* (p. 1597, figure 2C), raise in mammals immunized with it, IgG antibodies that can inhibit parasite growth *in vitro* in cooperation with human monocytes (claim 22), and also that said fragment is a synthetic peptide (claim 23).

Hanly *et al.* teach that with or without adjuvant, and within a window of immunogenicity, a larger dose of antigen generally results in a greater antibody response (p. 13, paragraph 3).

As to claims 19-23, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time of invention to combine, with a reasonable expectation of success, the synthetic $GLURP_{85-213}$ fragment of Theisen *et al.* and the MSP3 peptide, as well as a synthetic fragment of that peptide that includes the identified epitope ($MSP3_{211-237}$) of Oeuvray *et al.* into

the chimeric molecule and immunogenic composition of the instant application because Shi *et al.* teaches that combining these epitopes would create a multivalent synthetic (fusion) malaria vaccine with a higher level of protection that that provided by single component vaccine. Said combination of peptides would give a molecule that, when tested in the manner set forth in the instant specification, would raise higher levels of anti-MSP3 and anti-GLURP antibodies than a mixture of both $GLURP_{24-514}$ fragment and $MSP3_{212-380}$ fragment in mice immunized with it because Hanly *et al.* teaches that a larger dose of antigen generally results in a greater antibody response.

Claims 18, 27-28, are rejected under 35 U.S.C. 103(a) as being unpatentable over Druilhe *et al.* (U.S. Patent No. 6,017,538) in view of Theisen *et al.* (Infect. Immun. 69:5223-5229, 2001), and Shi *et al.* (Vaccine, 18:2902-2914, 2000).

Claim 18 is drawn to a chimeric molecule comprising a GLURP moiety comprising a variant of a polypeptide fragment of at least 50 amino acids from the $GLURP_{25-514}$ fragment and a MSP3 moiety comprising a polypeptide fragment of at least 50 amino acids from the $MSP3_{212-380}$ fragment wherein said chimeric molecule raises antibodies against both the $GLURP_{24-514}$ fragment and $MSP3_{212-380}$ fragment in mice immunized with it, wherein either or both moieties can have 1-15 amino acids deleted, added, or changed by conservative substitution. As such, a polypeptide comprising a GLURP moiety and an MSP3 moiety comprising 35 amino acids from SEQ ID 2 would meet the limitations of the claim. Claims 27 and 28 are drawn to an immunogenic composition comprising (claim 27) and a vaccine comprising as an immunogen (claim 28) the chimeric molecule of claim 18 or a conjugate comprising the chimeric molecule of claim 18 which is bound to a support.

Druilhe *et al.* teach (in claims 1, and 3-7) a purified MSP3 polypeptide fragment of 65 amino acids, 47 of which are 100% identical to residues 212-257 of SEQ ID 2. Druilhe *et al.* further teaches said molecule bound to a support (claim 8), as an immunogenic composition (claims 9-10), and as a vaccine (claim 11). Druilhe *et al.* differs from the instant application by not teaching the chimeric molecule as comprising both an MSP3 fragment and GLURP fragment wherein the chimeric molecule raises antibodies against both MSP3 and GLURP fragments.

Theisen *et al.* teach two synthetic GLURP fragments, $GLURP_{85-213}$ and $GLURP_{191-287}$ that raise, in mice immunized with them, antibodies to said fragments (p. 5224, col. 1, paragraph 2 and p. 5226, paragraph bridging columns 1 and 2).

Shi *et al.* teach that by combining epitopes identified through *in vitro* and *in vivo* studies in model systems, one can create a multivalent synthetic (fusion) malaria vaccine with a higher level of protection that that provided by single component vaccine (p. 2911, col. 2, paragraph 1).

As to claim 18 and 28-28, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time of invention to combine, with a reasonable expectation of success, the synthetic $GLURP_{85-213}$ fragment of Theisen *et al.* and the MSP3 polypeptide, as well as a synthetic fragment of that peptide that includes the identified epitope ($MSP3_{211-237}$) of Druilhe *et al.* into the chimeric molecule and immunogenic compositions of the instant application because Shi *et al.* teaches that combining these epitopes would create a multivalent synthetic (fusion) malaria vaccine with a higher level of protection that that provided by single component vaccine. Said combination of peptides would give a molecule that, when tested in the manner set forth in the instant specification, would raise anti-MSP3 and anti-GLURP in mice immunized with it.

Claims 18, 27-28, are rejected under 35 U.S.C. 103(a) as being unpatentable over Druilhe (U.S. Pat. Pub. 2004/0141987) in view of Theisen *et al.* (Infect. Immun. 69:5223-5229, 2001), and Shi *et al.* (Vaccine, 18:2902-2914, 2000).

Claim 18 is drawn to a chimeric molecule comprising a GLURP moiety comprising a variant of a polypeptide fragment of at least 50 amino acids from the $GLURP_{25-514}$ fragment and a MSP3 moiety comprising a polypeptide fragment of at least 50 amino acids from the $MSP3_{212-380}$ fragment wherein said chimeric molecule raises antibodies against both the $GLURP_{24-514}$ fragment and $MSP3_{212-380}$ fragment in mice immunized with it, wherein either or both moieties can have 1-15 amino acids deleted, added, or changed by conservative substitution. As such, a polypeptide comprising a GLURP moiety and an MSP3 moiety comprising 35 amino acids from SEQ ID 2 would meet the limitations of the claim. Claims 27 and 28 are drawn to an immunogenic composition comprising (claim 27) and a vaccine comprising as an immunogen (claim 28) the chimeric molecule of claim 18

Druilhe teaches (in claim 1) a purified MSP3 polypeptide fragment of 68 amino acids comprising a combination of the MSP-3b peptide (SEQ ID No: 12), MSP-3c peptide (SEQ ID No: 13), and MSP-3d peptide (SEQ ID No: 14), 67 of which are 100% identical to residues 212-228 of SEQ ID 2. Druilhe further teaches long synthetic or recombinant polypeptide comprising epitopes contained within a MSP-3b peptide (SEQ ID No: 12), a MSP-3c peptide (SEQ ID No: 13), or a MSP-3d peptide (SEQ ID No: 14) and combinations of said peptides (claim 2), an immunogenic composition comprising a long synthetic or recombinant polypeptide comprising epitopes contained within the MSP3b, MSP3c, or MSP3d polypeptides which together correspond to amino acids 212-278 of the MSP3 fragment of the instant application (claim 3), and a vaccine comprising said MSP3 molecule and a pharmaceutically acceptable carrier (claim 4). Druilhe *et al.* differs from the instant application by not teaching said peptides as a chimeric molecule comprising both an MSP3 fragment and GLURP fragment that raises antibodies against both MSP3 and GLURP fragments.

Theisen *et al.* teach two synthetic GLURP fragments, $GLURP_{85-213}$ and $GLURP_{191-287}$ that raise, in mice immunized with them, antibodies to said fragments (p. 5224, col. 1, paragraph 2 and p. 5226, paragraph bridging columns 1 and 2).

Shi *et al.* teach that by combining epitopes identified through *in vitro* and *in vivo* studies in model systems, one can create a multivalent synthetic (fusion) malaria vaccine with a higher level of protection that that provided by single component vaccine (p. 2911, col. 2, paragraph 1).

As to claims 18 and 27-28, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time of invention to combine, with a reasonable expectation of success, the synthetic $GLURP_{85-213}$ fragment of Theisen *et al.* and the MSP3 fragment polypeptide, of Druilhe into the chimeric molecule and immunogenic composition of the instant application because Shi *et al.* teaches that combining these epitopes would create a multivalent synthetic (fusion) malaria vaccine with a higher level of protection that that provided by single component vaccine. Said combination of peptides would give a molecule that, when tested in the manner set forth in the instant specification, would raise anti-MSP3 and anti-GLURP in mice immunized with it.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Benmohamed *et al.* Vaccine 18:2843-2855, 2000 and PCT Pub. WO 02/092628 A2.

### *Status of the Claims*

All claims stand rejected.

### *Conclusion*

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Gangle whose telephone number is 571-272-1181. The examiner can normally be reached on M-F 8:00 am - 4:30 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on 571-272-0864.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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